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A Molecular Dynamics Investigation on the Inclusion of Chiral Agrochemical Molecules in β-Cyclodextrin. Complexes with Dichlorprop, 2-Phenoxypropionic Acid and Dioxabenzofos

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Abstract: Cyclodextrins are a group of cyclic oligosaccharides with a ring, basket-like structure. These compounds are able to include several kinds of molecules into their internal cavity, leading to important modifications of the properties of the guest compound.

The interaction between β-cyclodextrin and the *R* and *S* enantiomers of dichlorprop, 2-phenoxypropionic acid and dioxabenzofos was investigated by means of molecular dynamics (MD). Several *in vacuo* trajectories were calculated for each system imposing a 1 : 1 stoichiometry. The results account for the formation of adducts which are stable at room temperature. The analysis of statistical data from the MD runs shows that dioxabenzofos exhibits the weakest interaction in the series studied and that the *R* and *S* enantiomers of dichlorprop and phenoxypropionic acid interact in a different fashion with the host molecule. © 1998 Society of Chemical Industry

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Key words: enantioselective binding; pesticides; molecular modelling

1 INTRODUCTION

Cyclodextrins are cyclic oligomers of 1-4 linked α-D-glucose monomers which form inclusion complexes with several molecules. The interaction with the cyclodextrin molecule leads to important modifications of the properties of the guest compound, allowing the fixation of volatile materials, protection against oxidation and photolysis, modification of reactivity and of biological properties. Owing to this ability, cyclodextrins have been the subject of a considerable number of studies in the past two decades.[1–3] Most of these studies have focused on the inclusion complexes of cyclodextrins as well as on the use of these molecules as an environment of chemical reactions.[4–6] More recently, these molecules have been employed in chromatography to separate constitutional isomers and enantiomers.[7,8] As a consequence, these molecules are of great interest to a wide range of scientists in most fields of chemistry.

The structural features of cyclodextrins have also been investigated. Such studies mainly deal with the inclusion complexes in the solid state[9–11] or in solution phase.[12] In recent years a number of theoretical investigations have been reported,[13–20] most of which focused on the study of the interactions between the β-cyclodextrin (BCD) molecule and small ligand molecules. In order to evaluate the ability of BCD to discriminate between different enantiomers of pesticides we have used molecular modelling techniques to investigate the mechanism of selective binding. In this study we present the results of a series of molecular dynamics

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experiments carried out on the inclusion complexes of BCD with the *R* or *S* enantiomers of dichlorprop, 2-phenoxypropionic acid and dioxabenzofos.

2 MATERIALS AND METHODS

The BCD host molecule is shown in Fig. 1. It consists of seven D-glucopyranose monomers connected by α-(1-4) linkages. Topologically this molecule can be represented by a toroid in which the primary and secondary hydroxyl groups are placed on the smallest and the largest circumferences, respectively. No hydroxyl group is present within the toroid cavity which, accordingly, has a pronounced hydrophobic character.

The guest molecules are shown in Fig. 2. The 2-phenoxypropionic acid and the dichlorprop molecules show structural analogies as both have a phenyl ring with a tail bearing a carboxylic function at its end, and they may be expected to exhibit similar behaviour. The molecules were constructed by means of the molecular editor of the Chem-X suite of programs. Each enantiomer was then docked to the BCD cavity in order to form a 1 : 1 complex. Six complexes were formed, one for each of the enantiomers taken into account. These adducts were used as starting points in the molecular dynamics (MD) experiments.

Molecular dynamics (MD) is a computer simulation technique where the time evolution of a set of interacting atoms and/or molecules is predicted by integrating their equations of motion.

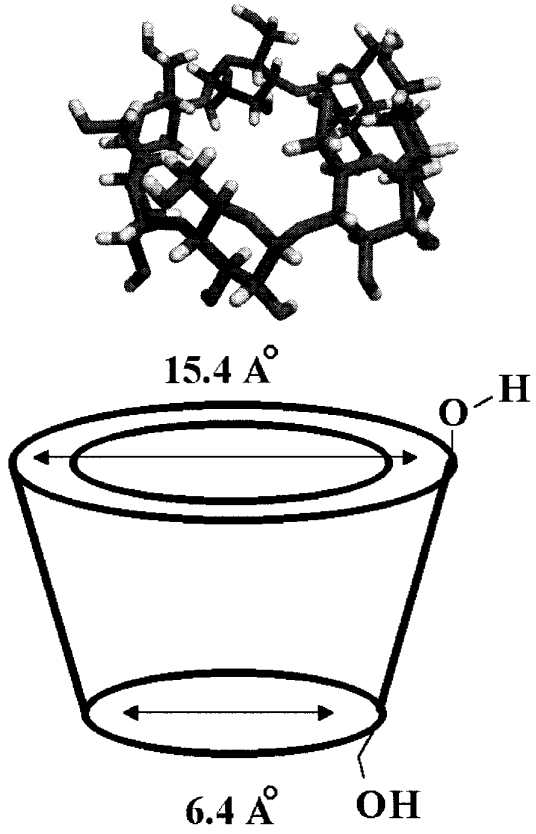
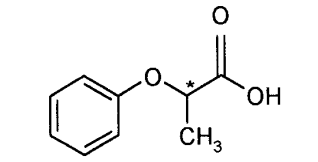
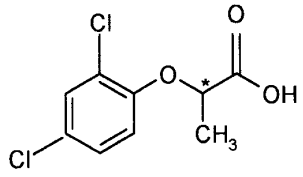


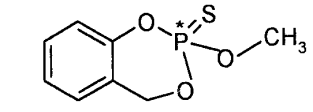
Fig. 1. The β-cyclodextrin molecule and its schematic representation.



2–Phenoxypropionic acid



Dichlorprop



Dioxabenzofos

Fig. 2. Structures of the guest molecules. A star (*) is used to mark the stereo centres.

In a molecular dynamics experiment the equation of motion for each particle follows the laws of classical mechanics, and most notably Newton's law:

$$F_i = m_i a_i \tag{1}$$

for each atom i in a system constituted of N atoms.

Here, m_i is the atom mass, $a_i = d^2r_i/dt^2$ its acceleration, and F_i the force acting upon it, due to the interactions with other atoms.

The rate and direction of motion (velocity) are governed by the forces that the atoms of the system exert on each other as described by Newton's equation (1). In practice, the atoms are assigned initial velocities that conform to the total kinetic energy of the system, which, in turn, is dictated by the desired simulation temperature. This is carried out by slowly 'heating' the system (initially at absolute zero) and then allowing the energy to equilibrate among the constituent atoms. The basic ingredients of molecular dynamics are the calculation of the force on each atom, and from that information, the position of each atom throughout a specified period of time (typically on the order of picoseconds = 10^{-12} seconds).

The force on an atom can be calculated from the change in energy between its current position and its position a small distance away. This can be recognised as the derivative of the energy with respect to the change in the atom's position:

$$F_i = -\nabla V(r_1, \ldots, r_N) \tag{2}$$

This form implies the presence of a conservation law of the total energy $E = K + V$, where K is the instantaneous kinetic energy.

Knowledge of the atomic forces and masses can then be used to solve the equations to give the positions of each atom along a series of extremely small time steps (of the order of femtoseconds $= 10^{-15}$ seconds). The resulting series of snapshots of structural changes over time is called a trajectory.

In practice, trajectories are not directly obtained from Newton's equation, due to lack of an analytical solution. First, the atomic accelerations are computed from the forces and masses. The velocities are next calculated from the accelerations, lastly, the positions are calculated from the velocities.

A trajectory between two states can be subdivided into a series of sub-states separated by a small time step, Δt (e.g. 1 femtosecond):

The initial atomic positions at time t are used to predict the atomic positions at time $t + \Delta t$. The positions at $t + \Delta t$ are used to predict the positions at $t + 2\Delta t$ and so on.

Therefore molecular dynamics is a deterministic technique: given an initial set of positions and velocities, the subsequent time evolution is *in principle* completely determined. The computer calculates a trajectory in a $6N$-dimensional phase space ($3N$ positions and $3N$ momenta). However, such a trajectory is usually not particularly relevant by itself. *Molecular dynamics is a statistical mechanics method.* Like Monte Carlo, it is a means of obtaining a set of configurations distributed according to some statistical distribution function, or statistical ensemble.

According to statistical physics, physical quantities are represented by averages over configurations distributed according to a certain statistical ensemble. A trajectory obtained by molecular dynamics provides such a set of configurations. Therefore, a measurement of a physical quantity by simulation is obtained simply as an arithmetic average of the various instantaneous values assumed by that quantity during the MD run.

Statistical physics is the link between microscopic behaviour and thermodynamics. In the limit of very long simulation times, one could expect the phase space to be fully sampled, and in that limit this averaging process would yield the thermodynamic properties. In practice, the runs are always of finite length, and one should be cautious in estimating whether a sufficient sampling has been achieved (i.e. the system has reached equilibrium) or not.

The corner stone of a simulation procedure is the model we choose to describe the physical system we want to reproduce. For a molecular dynamics simulation this corresponds to choosing the *potential:* a function $V(r_1, \ldots, r_N)$ of the positions of the nuclei, representing the potential energy of the system for each specific configuration. This function is translationally and rotationally invariant, and is usually constructed from the *relative* positions of the atoms with respect to each other, rather than from the absolute positions.

The problem of modelling a chemical system can therefore be restated as that of finding a potential function $V(r_1, \ldots, r_N)$ or *force field* (FF) for that system. This function returns energy as a function of conformation.

Typically, force fields are sums of terms which correspond to bond, angle, torsion, vdw and electrostatic interaction energies as functions of conformation:

$$V_{\text{conformation}} = E_{\text{bonds}} + E_{\text{angles}} + E_{\text{torsions}} + E_{\text{vdw}} + E_{\text{electrostatic}}$$

The mathematical form of the energy terms varies from force field to force field. Most commonly, the terms are summations of the following form:

$$\begin{aligned} V(r_1, \ldots, r_N) = {} & \tfrac{1}{2} \sum k_\rho(\rho_0 - \rho)^2 + E_{\text{bonds}} \\ & + \tfrac{1}{2} \sum k_\theta - \theta)^2 + E_{\text{angles}} \\ & + \tfrac{1}{2} \sum k_\phi(\phi_0 - \phi)^2 + E_{\text{torsions}} \\ & + \sum (A/r^{12} - B/r^6 + q_1 q_2/Dr) \\ & \times (E_{\text{vdw}} + E_{\text{elect.}}) \end{aligned} \tag{3}$$

The stretching (bond), bending (angle) and torsion energy equations are based on Hooke's law. The parameter k controls the stiffness of the spring, while ρ_0, θ_0, and ϕ_0 define its equilibrium value.

The last term in eqn (3) accounts for repulsion, van der Waals attraction, and electrostatic interactions. The van der Waals attraction occurs at short range, and rapidly dies off as the interacting atoms move apart by a few Angstroms. Repulsion occurs when the distance between interacting atoms becomes even slightly less than the sum of their contact radii. Repulsion is modeled by an equation that is designed to rapidly blow up at close distances ($1/r^{12}$ dependency). The energy term that describes attraction/repulsion provides for a smooth transition between these two regimes.

The A and B parameters control the depth and position (interatomic distance) of the potential energy well for a given pair of non-bonded interacting atoms (e.g. C : C, O : C, O : H, etc).

The parameter A can be obtained from atomic polarizability measurements, or it can be calculated quantum mechanically. The parameter B is typically derived from crystallographic data so as to reproduce observed average contact distances between different kinds of atoms in crystals of various molecules.

The electrostatic contribution is modeled using a Coulombic potential. The electrostatic energy is a function of the charge on the non-bonded atoms, their interatomic distance, and a molecular dielectric expression that accounts for the attenuation of electrostatic interaction by the environment (e.g. solvent or the molecule

itself). Partial atomic charges can be calculated for small molecules using an *ab initio* or semiempirical quantum mechanics program.

The bond, angle, and torsion terms are summed over all bonds, angles, and torsions. The vdw and electrostatic terms are summed over all possible pairs of atoms. Typically, the electrostatic contribution dominates the total energy of a system by a full magnitude. The molecules are represented in force fields as a collection of charged point masses which correspond to atomic centres.

2.1 Computational Details

The MD runs were performed employing the DLPOLY2[21] program. The AMBER plus GLYCAM[22] force field was used with the necessary adaptations, while the BCD partial atomic charges were calculated by the Gasteiger method.[23] In the simulation all the atoms and molecules are free to move and all the atoms are treated explicitly. The starting BCD structure for the simulation was taken from the 'BCDEX04' entry of the Cambridge Crystallographic Database. The systems were coupled to a thermal bath of $T_0 = 298$ K using a temperature relaxation times of 0·1 ps. This value makes the temperature coupling weak enough to avoid any significant effect on the atomic properties of the system.[14] Calculations were carried out on IBM RS6000 and HP9000 computers at the Department of CNR location.

All the MD simulations on the different host-guest couples were performed in the NVT ensemble (number of particles, volume and temperature held constant) inside a 35 Å cubic cell at a temperature of 298 K. The system was allowed to equilibrate for 200 ps and then the trajectory was collected over 1000 ps.

2.2 Experimental

BCD inclusion complexes of dichlorprop, 2-phenoxypropionic acid and dioxabenzofos were prepared in aqueous solution using the following general procedure. BCD (5 mg, 0·44 mmol) was dissolved in degassed distilled water (10 ml) under an argon atmosphere at 70°C for 1 h. Thereupon one equivalent of guest compound was added in one pot. The solution immediately became opalescent and turned milky after few hours of stirring at 70°C.

At different times, an aliquot of the mixture was analysed by NMR. The solution was separated from the solid, when present, and roto-evaporated to dryness under vacuum. BCD forms stable complexes with both dichlorprop and 2-phenoxypropionic acid after 7 h at 70°C and after 24 h at room temperature. No experimental evidence has been observed for a BCD dioxabenzofos complex.

3 RESULTS AND DISCUSSION

Snapshots of the equilibrium configurations of the complexes are shown in Fig. 3. The plots indicate that the guest molecules approach the BCD ring with their molecular axes almost parallel to the BCD molecule diameter. The carboxylic end of dichlorprop and 2-phenoxypropionic acid points toward the BCD cavity and forms hydrogen bonds with the hydroxyls and the non-hydroxylic (etheric) oxygen atoms of the cavity. All the guest molecules access the cavity by the top torus side. It can be observed that both the *R* and *S* enantiomers of the dioxabenzofos molecule move outside the BCD ring; this poor interaction is particularly clear for the *R*-enantiomer.

Total energy values, averaged over the 1000 ps run, were recorded for each of the above systems. The conformational energy differences between the adducts with the *R* and the *S* enantiomers are reported in Table 1 for each of the compounds studied. The adduct with the *S* enantiomer is more stable than that with the *R* by 4·33, 7·78 and 34·83 kcal mol^{-1} for dichlorprop, 2-phenoxypropionic acid and dioxabenzofos, respectively. Table 1 also reports the values of ΔE_{s-r} broken down according to contributions due to the bond, angle, torsion, van der Waals and Coulomb energies.

The atom types of the BCD molecule are shown in Fig. 4. The computed radial distribution functions (g(*r*)) among the atoms in the BCD and in the guest molecules are shown in Figs 5–8. The g(*r*) function gives the probability of finding a pair of the atoms at a distance *r*,

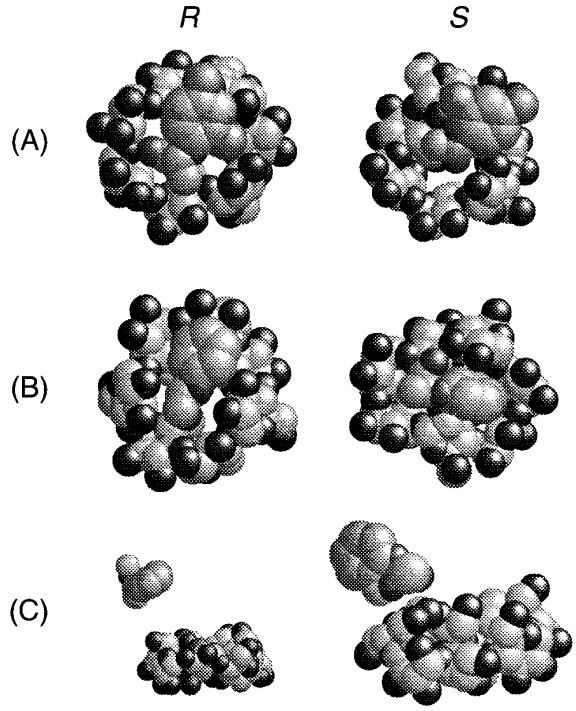


Fig. 3. Equilibrium conformation of BCD-guest complexes. (A) dichlorprop (B) 2-phenoxypropionic acid, (C) dioxabenzofos.

TABLE 1
Energy Differences between the Complexes of BCD with the *R* and *S* Enantiomers for Each of the Considered Molecules (kcal mol^{-1})

	ΔE_{s-r}		
	2-Phenoxypropionic acid	Dichlorprop	Dioxabenzofos
E_{conf}	−4·78	−7·78	−34·83
E_{b+a+t}	−5·16	−6·89	−30·51
E_{vdw}	+1·56	+0·67	−1·92
E_{coul}	−0·73	−1·56	−2·4

The terms E_{coul}, E_{vdw}, and E_{b+a+t} refer to the electrostatic, van der Waals, and bond + angle + torsion contributions to the total conformational energy (E_{conf}).
$E_{conformation} = E_{bonds} + E_{angles} + E_{torsions} + E_{vdw} + E_{coulomb}$

relative to the probability expected for a completely randomly distributed sample at the same density.

The gCT-CA radial distribution functions (Fig. 5) between the carbon atoms in the BCD ring and the carbon atoms in the aromatic ring of the guest molecules show a peak at about 5 Å, corresponding to the mean distance between the two atom types. The peak is slightly shifted to the left for each of the *S* enantiomers, thus evidencing a closer interaction between the BCD and the *S* enantiomers; moreover, the plots elucidate the poor interaction between the BCD and the *R*-dioxabenzofos molecule.

The values of g(*r*) between the BCD hydroxyl functions and the acid OH groups in the guest molecules are shown in Fig. 6. The plots account for the formation of hydrogen bonds between the host and the guest compounds. The *R* and *S* enantiomers of dichlorprop and the *R* 2-phenoxypropionic acid exhibit a similar behaviour, forming preferential H-bonds oriented towards the secondary BCD hydroxyl groups. The van der Waals contribution to the total energy is rather similar for the above compounds (*c.* 7 kcal mol^{-1}). The *S*-2-phenoxypropionic acid exhibits the poorest van der Waals interaction in this group (*c.* 5 kcal mol^{-1}); this is shown by the plots in Fig. 6.

The plots in Fig. 7 show the g(*r*) between the etheric O atoms in the BCD ring (O4 and O5) and the acid OH groups of the dichlorprop and 2-phenoxypropionic acid.

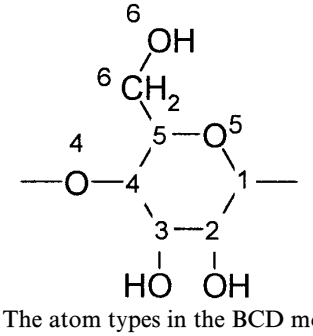


Fig. 4. The atom types in the BCD monomer.

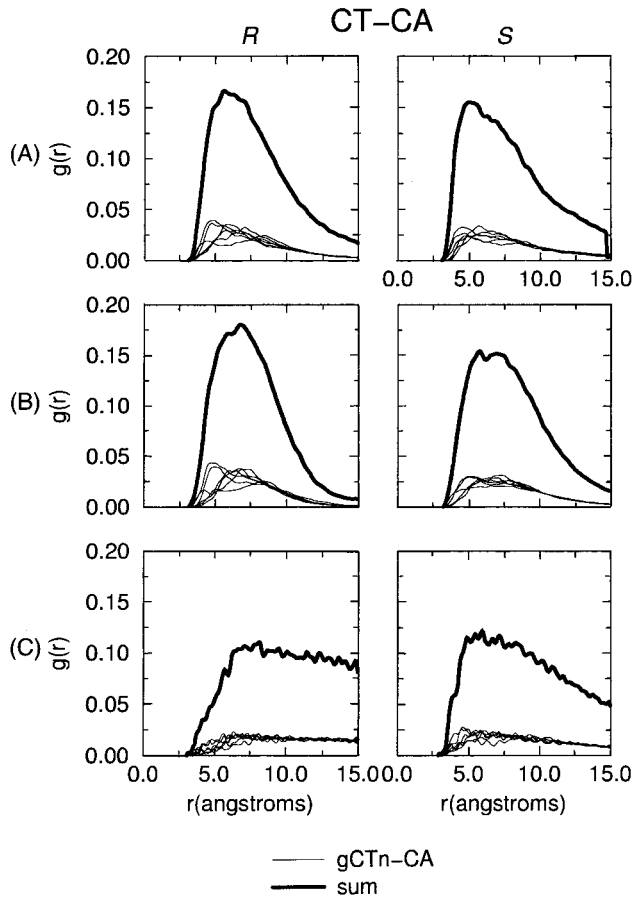


Fig. 5. Radial distribution functions between the CT type atom in BCD and the aromatic carbon atoms of the guest molecules. (A) 2-phenoxypropionic acid, (B) dichlorprop, (C) dioxabenzofos.

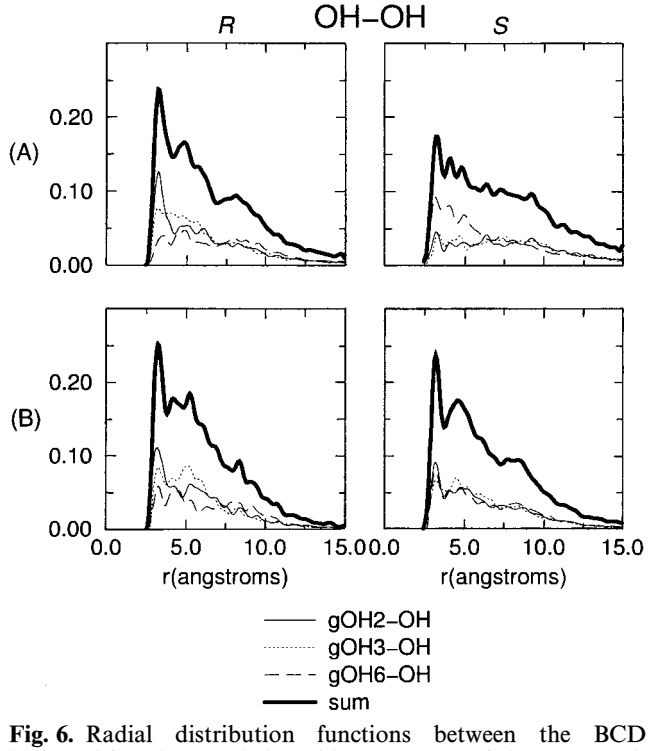


Fig. 6. Radial distribution functions between the BCD hydroxyl functions and the acid OH groups of the guest molecules. (A) 2-phenoxypropionic acid, (B) dichlorprop.

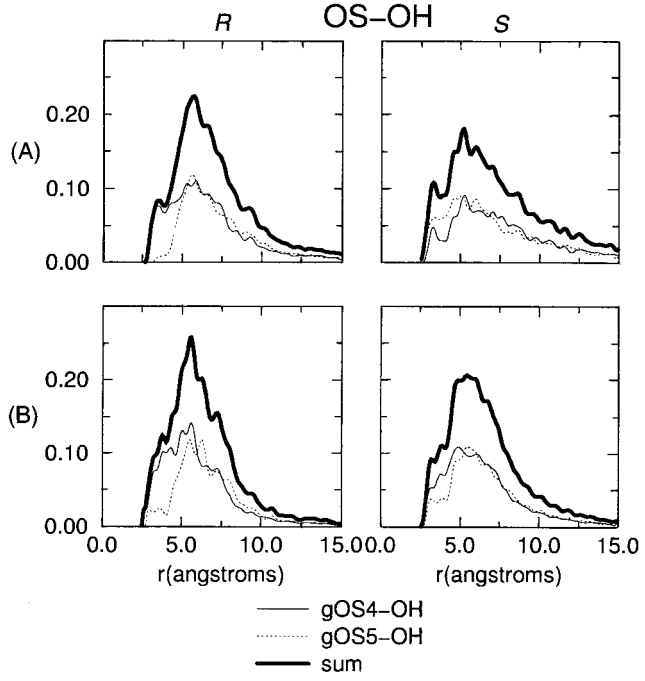


Fig. 7. Radial distribution functions between the BCD O4 and O5 atoms and the acid OH groups of the guest molecules. (A) 2-phenoxypropionic acid, (B) dichlorprop.

The plots show a first peak at about 3 Å, due to the formation of hydrogen bonds between the hydroxyl of the guest molecule and the etheric oxygens in the BCD. The *R* enantiomers form H-bonds only with the O4 type atoms of the BCD, while the *S* enantiomers interact to a similar extent with both the etheric oxygen atom types of the BCD ring (O4 and O5).

As a general trend, the *R* enantiomers of both dichlorprop and 2-phenoxypropionic acid form stronger hydrogen bonds with the BCD oxygen than do the *S* ones. However, the complexes with the latter are more stable. Inspection of the contributions to the ΔE_{s-r} values (Table 1) shows that the increased stability of the *S* adducts is due to the gain in conformational energy of the BCD-guest system, i.e. the release of strain energy in the BCD molecule.

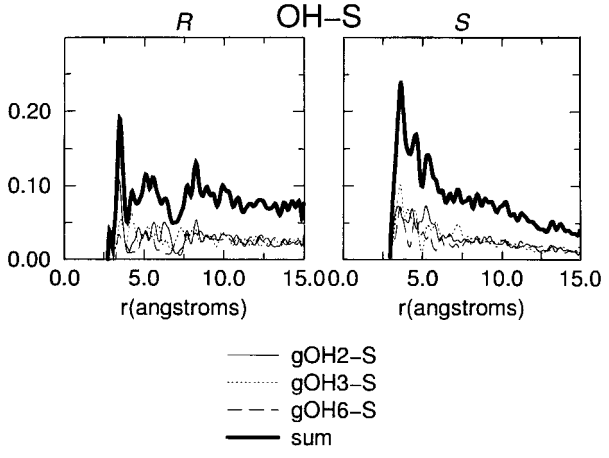


Fig. 8. Radial distribution functions between the BCD OH atoms and the sulfur atom of the dioxabenzofos molecule.

The plots in Fig. 8 show the formation of hydrogen bonds between the ring hydroxyls of the BCD molecule and the sulfur atom in the dioxabenzofos molecule. It is well evidenced that the *S*- enantiomer plot shows better defined and sharper peaks, thus accounting for its higher interaction energy with the BCD molecule.

4 CONCLUSIONS

An analysis of the interactions between BCD and the *R* and *S* enantiomers of dichlorprop, dioxabenzofos and 2-phenoxypropionic acid has been undertaken by means of molecular dynamics. The results account for the formation of adducts with the dichlorprop and the 2-phenoxypropionic acid molecules which are stable at room temperature, while neither of the dioxabenzofos enantiomers entered the BCD cavity completely, so that the adducts appeared to be very weak.

The energetic data established that, as a general rule, the BCD molecule shows a preference for *S* enantiomers. The plots of the radial distribution functions show that the *R* enantiomers form hydrogen bonds mainly with the oxygen atoms of the secondary hydroxyl groups (O2 and O3) in the BCD molecule, while the *S* enantiomers form H-bonds even with the oxygens in the primary hydroxyl groups (O6) of the BCD molecule. The analysis of the energy data reveals that the complexes with the *R* enantiomers of dichlorprop and 2-phenoxypropionic acid exhibit a more advantageous hydrogen bond network, and that the formation of adducts with the *S* enantiomers is favoured by the release of strain energy mainly by the BCD molecule.

ACKNOWLEDGEMENTS

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